REMARKS

Reconsideration of the rejections set forth in the Office Action dated September 29, 2005 is respectfully requested. Applicants petition for a one-month extension of time and a separate petition is attached. Claims 1-4 and 16-17 are pending.

I. Amendments

A. Amendments to the Specification

The application has been amended to remove a claim to the benefit of co-pending U.S. Application No. 09/910,406, filed July 19, 2001; to U.S. Provisional Application No. 60/219,128, filed July 19, 2000; and to Japanese Application No. 317160 filed October 17, 2000.

Removal of the priority claims brings the Applicant in compliance with 37 C.F.R. § 1.63(c).

Typographical errors in paragraph [0087] are corrected.

B. Amendments to the Claims

Claim 1 is amended to recite that the claimed method is directed to the treatment of multiple sclerosis in a human subject, as disclosed, for example, in paragraph [0062] by orally administering a daily dose of at least about 9×10^8 Units, as disclosed, for example, in paragraphs [0080] or [0091] in view of paragraph [0107].

Claim 4 is amended to clarify that the interferon-tau is administered orally in a dosage form designed for administration of the protein to the intestinal tract. Basis is found in paragraph [0128].

Claims 5-15 stand canceled.

Claim 17 is amended for consistency with claim 1.

II. Rejections Under 35 U.S.C. §112

A. Rejection under 35 U.S.C. §112, second paragraph

Claim 4 was rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which

Applicants regard as the invention. Specifically, the Examiner asserted that the language in claim 4 was confusing.

Claim 4 is amended to clarify that a dosage form of interferon-tau is administered orally, for release in the intestinal tract.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

B. Rejection under 35 U.S.C. §112, first paragraph

Claims 1-17 were rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. As basis for the rejection, the Examiner alleges that (1) the guidance in the specification as to what dose to use is not sufficient to indicate the dose necessary for achieving increased IL-10 in the wide variety of disease conditions recited in the claims, and (2) there is no working example that demonstrates achieving a desired clinical endpoint. This rejection is traversed in view of the foregoing claim amendments and following remarks, including those made in reference to the attached Declaration of Dr. Norman Kachuck.

Claims 1-4, 16, and 17, as now amended, are directed to a method of treating multiple sclerosis, by orally administering interferon-tau at a daily dose of at least about 9×10^8 Units, and continuing to administer at this dose level until a desired end point is reached.

As set forth in the attached Kachuck Declaration, Dr. Kachuck is a principal investigator in an ongoing clinical study to evaluate, *inter alia,* the efficacy of orally administered interferon-tau on the symptoms and disease state of persons previously diagnosed with multiple sclerosis (Kachuck Declaration ¶ 7). In the clinical study, multiple sclerosis patients were, and continue to be, treated with interferon-tau at a daily dose of 9×10^8 Units (Kachuck Declaration ¶ 9). The fifteen patients enrolled in the study have completed six months of treatment with interferon-tau.

To evaluate the efficacy of orally-administered interferon-tau, magnetic resonance imaging (MRI) brain scans of the patients were taken monthly to evaluate the number of new gadolinium-enhancing lesions (Kachuck Declaration ¶¶ 8, 10). Prior to initiation of treatment with interferon-tau, MRI brain scans of each patient were done to

provide an average pre-treatment baseline number of new gadolinium-enhancing lesions (Kachuck Declaration ¶ 8). Treatment with interferon-tau at a daily dose of at least about 9×10^8 Units was effective to reduce the number of new gadolinium-enhancing lesions in a majority of patients (Kachuck Declaration ¶¶ 11-13). As stated in the Kachuck Declaration, the ability to substantially eliminate new lesions in a majority of patients with active MS represents a significant and important improvement in MS treatment.

In view of the claim amendments and the additional evidence that demonstrates achieving a desired clinical endpoint, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

III. Rejections Under 35 U.S.C. §103

Claims 1-3 and 5-7, prior to the current amendments, were rejected under 35 U.S.C. §103 as allegedly obvious over Soos *et al.*, U.S. Patent No. 6,060,450 (hereinafter "Soos '450").

Claims 1-3, 5, 6, 16, and 17, prior to the current amendments, were rejected under 35 U.S.C. §103 as allegedly obvious over Soos *et al.* (*J. Immunology*, 169:2231 (2002), hereinafter "Soos *et al.*".)

To the extent these rejections apply to the currently amended claims, the rejections are respectfully traversed for the following reasons.

A. The Present Claims

The present claims relate to a method of treating multiple sclerosis (MS) in a human subject. MS is a non-contagious, lifelong chronic disease that causes symptoms such as weakness, muscle stiffness, poor coordination and balance, tingling, numbness, tremors, blurred vision, and slurred speech. An estimated 400,000 Americans have MS, according to the National Multiple Sclerosis Society (NMSS). Every week, about 200 people in the United States are diagnosed with the disease (http://www.fda.gov/fdac/features/2005/205_ms.html, visited on November 16, 2005).

Today, there are five[1] FDA-approved drugs to lessen the likelihood of MS attacks on the market. These drugs have limited effectiveness in treating MS and are inconvenient because they must be taken via injection (http://www.fda.gov/fdac/features/2005/205_ms.html, visited on November 16, 2005). The currently-available drugs are also toxic and cause unwanted side effects (Id.). For example, the approved interferon-beta compounds (Avonex®, Betaseron®, Rebif®) cause flu-like symptoms and reactions at the injection site. Copaxone® gives short term reactions of flushing, chest pain, heart palpitations, anxiety, and shortness of breath (Id.).

Another problem associated with the current interferon-beta therapies for MS is the induction of neutralizing antibodies ((Killestein, J. *et al., Current Opin. in Neurology*, 18:253 (2005)). Neutralizing antibodies to interferon-beta reduce interferon-beta bioavailability and therapeutic efficacy (Id.). Researchers are currently conducting studies to understand the effect of dose and frequency of dosing on neutralizing antibody formation to understand whether an optimal interferon-beta regimen (dose and dosing frequency) can be identified (Id.).

It is also reported in the literature that despite some beneficial effects of the currently available treatments, all the treatments are only partially effective in treating MS (Kappos, L. *et al., J. Neurol.*, 251[Suppl 5]:V57-V64 (2004)). Moreover, the efficacy of the treatments have been shown to be dependent on dose and dose frequency, suggesting that for treatment of MS, appropriate dose selection is critical (Id.).

The present inventors have found that oral administration of interferon-tau, a protein that is not found in humans, at a dose of at least about 9×10^8 Units/day and over an extended time period, provides a beneficial reduction in new brain lesions, as discussed more fully in the Kachuck Declaration.

[1]The five treatments are Avonex (interferon beta-1a, Biogen Idec, Inc.); Betaseron (interferon beta-1b, Berlex Laboratories, Inc.); Rebif, (interferon-beta 1a, Serono Inc.); Copaxone (glatimer acetate, Teva NeuroScience Inc.); Novatrone (mitoxantrone, Serono Inc.). A sixth compound, Tysabri (natalizumab, Biogen Idec, Inc.), was approved by the FDA but was voluntarily suspended from the market in Feb. 2005 due to two serious adverse events, including one death.

B. The Cited Art

Soos '450 discloses a method for treating autoimmune disorders by administering interferon-tau. Soos '450 discloses on Col. 14, lines 25-29:

> "interferon-tau can be administered at doses from about 5 x 10^4 to 20 x 10^6 units/day to about 500 x 10^6 units/day or more. In a preferred embodiment, the dosage is about 10^6 units/day. High doses are preferred for systemic administration."

Soos *et al.* disclose oral administration of interferon-tau to mice induced to develop experimental allergic/autoimmune encephalomyelitis (EAE) at various doses ranging from 1 x 10^4 to 1 x 10^5 Units/day.

C1. Analysis: Rejection Over Soos '450

As noted above, the present claims relate to oral administration of interferon-tau at a dose of at least about 9 x 10^8 Units/day to achieve a desirable clinical outcome in human MS patients.

Soos '450 discloses a dose range of "5 x 10^4 to 20 x 10^6 to about 500 x 10^6 units/day or more". Applicants submit that disclosure of this broad dosage range does not render obvious the present claims for at least the following reasons.

First, the teaching in Soos '450 does not guide one to the presently claimed dose of at least about 9 x 10^8 Units, which is beyond the uppermost value of the of the range disclosed. The teaching of a specified range followed by the words "or more" cannot be taken as a meaningful guide to any particular dose.

For selection of a dose based on the broad range disclosed in Soos '450, one might look to the doses exemplified in the EAE mouse model studies (3 x 10^5 units) or to the mention in Soos '450 that "high doses are preferred for systemic administration" (Col. 14, lines 29-30). With respect to any alleged guidance from the dose used in the mouse EAE studies, the exemplified dose of 3 x 10^5 units is well below the claimed dose, even after taking into account body weight differences between a mouse and a human.

Second, the scientific literature (e.g., Kappos, L. *et al., J. Neurol.*, 251[Suppl 5]:V57-V64 (2004)), discussed above, suggests that dose selection is an important feature of treatment regimens for MS. A skilled person looking to Soos '450 for

guidance in an effective dose would be led to try the doses exemplified in Soos '450 – namely doses in the range of 10^5 U/day and administered via injection. Soos '450 provides no guidance as to which dose would be effective when administered orally or to which dose when administered orally would be effective to provide a desirable treatment outcome in humans.

Since nothing in the teaching of Soos '450 guides a skilled practitioner to the claimed dosage range, nor to the claimed dosage range for the oral mode of administration, in the treatment of MS in humans, the claimed invention is not obvious over Soos '450. Accordingly, Applicants repectfully request withdrawal of the rejection under 35 U.S.C. §103.

C2. Analysis: Rejection Over Soos *et al.*

The Examiner asserts that it would have been within the ordinary skill of the art based on the teachings of Soos *et al.* to modify and optimize the dosage for a human, with reasonable expectation of success. Applicants submit that the teaching in Soos *et al.* fails to show all of the claim features and does not suggest all of the claim features.

Soos *et al.* disclose oral administration of interferon-tau to EAE model mice, where 1×10^5 Units/day is the highest dose for which data is shown. As noted above, a dose of 1×10^5 Units is below the claimed dose, even after taking into account body weight differences between a mouse and a human. Thus, Soos *et al.* does not show all of the claim features.

Moreover, Soos *et al.* nowhere suggest a dose of interferon-tau at the dosage range presently claimed. Thus, Soos *et al.* do not suggest all of the claim features.

Further, the Examiner's argument that *Soos et al.* could be modified with a "reasonable expectation of success," is without basis. Nothing in the teaching of Soos *et al.* would guide one to the presently claimed dose. Nor is there any teaching in Soos *et al.* from which a skilled practitioner would base an expectation that the presently claimed dosage range would provide a favorable clinical outcome in human MS patients, as the disclosure in Soos *et al.* is limited to mouse studies at considerably lower doses. The applicants were the first to demonstrate that interferon-tau, when administered orally to human at a dose of at least about 9×10^8 U/day, is effective in

treatment of MS in humans. The teaching in Soos *et al.* does not provide any expectation of this result at the claimed dose.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

IV. Double-Patenting Rejections

Claims 1, 8, 12, and 13 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 18-26 of application serial no. 09/910,406. Applicants respectfully traverse this rejection.

Claims 1-13 and 16-17 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 of application serial no. 10/825,382.

Claims 1-17 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-11 of application serial no. 10/825,457.

Claims 16-17 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-34 of application serial no. 10/884,741.

Claims 1-17 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 2, 5-9, 12, 25, and 30-32 of application serial no. 11/040,706.

A Terminal Disclaimer prepared in accordance with 37 C.F.R. §1.321(b) and (c) is enclosed. The signed Terminal Disclaimer obviates the obviousness-type double patenting rejections based on the 10/825,382, 10/825,457, 10/884,741, and 11/040,706 applications.

Claims 1-17 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-12 of application serial no. 11/078,608. Applicants respectfully traverse this rejection.

A. Legal Standard

In determining whether a non-statutory basis exists for a double patenting rejection, the first question to be asked is - does any claim in the application define merely an invention that is merely an obvious of an invention claimed in the patent?. M.P.E.P. 804 II.B.1.

A double patenting rejection of the obviousness type is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. § 103 except that the patent principally underlying the double patenting rejection is not considered prior art. M.P.E.P. 804 II.B.1.

B. Analysis

The obviousness-type double patenting rejections with respect to the '382, '457, '741, and '706 applications are overcome by submission of a Terminal Disclaimer, enclosed herewith. Rejection of the present claims in view of the '406 and '608 applications is traversed for the following reasons.

B1. Analysis of Rejection Over Claims 18-26 of Application Serial No. 09/910,406

Instant claims 1, 8, 12, and 13 were rejected as being an obvious variation of claims 18-26 of application serial no. 09/910,406 ("the '406 application").

Instant claims 8, 12, and 13 stand canceled. Claim 1 relates to a method of treating multiple sclerosis in a human subject by orally administering interferon-tau at a daily dose of at least about 9×10^8 Units.

Pending claims 18-26 of the '406 application are directed to a method for decreasing the alanine transferase (ALT) blood level in a human subject by orally administering interferon-tau.

Applicants submit that a method of treating multiple sclerosis in a human subject is not an obvious variation of a method of decreasing ALT blood levels, which are

elevated typically in a person with a viral infection, such as hepatitis C. One skilled in the art would not reasonably believe that a method of treating multiple sclerosis by administering interferon-tau is an obvious variation of a method of decreasing ALT blood levels by administering interferon-tau.

Accordingly, withdrawal of the obviousness-type double patenting rejection over the '406 application is respectfully requested.

B2. Analysis of Rejection Over Claims 1-12 of Application Serial No. 11/078,608

Claim 1 relates to a method of treating multiple sclerosis in a human subject by orally administering interferon-tau at a daily dose of at least about 9×10^8 Units, and continuing to orally administer interferon-tau to the subject until a desired clinical endpoint is achieved.

Pending claims 1-12 of the '608 application are directed to an improvement in the treatment of a human disease or condition responsive to continued and periodic interferon-tau administration. The method includes administering a therapeutically indicated amount of interferon-tau at each of a plurality of time points over a given time period. The method of the '608 application further includes adjusting the dose of interferon-tau administered based on the IL-10 response measured.

One skilled in the art would not reasonably find the present method including a step of continuing to orally administer interferon-tau until a clinical endpoint is reached an obvious variation of a method that includes steps of measuring the level of serum IL-10 and adjusting the dose of interferon-tau based on the subject's IL-10 response.

Accordingly, withdrawal of the obviousness-type double patenting rejection over the '608 application is respectfully requested.

V. Conclusion

In view of the above remarks, the applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 324-0880.

Respectfully submitted,

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Date: 1/30/06

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